The dawning of molecular genetics

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In February 1944, I was shuttling between service as a hospital corpsman at a US Naval Hospital and the completion of my pre-medical studies at Columbia College in New York. I was just short of 19, and in uniform in the Navy V-12 officers' training program. At Columbia, as an undergraduate I had already worked for two years in the laboratory of Francis J. Ryan, among the first of the league of students and followers of George Beadle and Edward L. Tatum, the pioneers of the biochemical genetics of *Neurospora*. Our main preoccupation at that moment was probably the faltering beachhead at Anzio, the invasion of Italy and the breathless anticipation of the Normandy invasion, the D-Day that was to come on June 6, 1944: the hinge of history that would tell the outcome of the war against Hitler.

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However, February 1, 1944 was the date of publication of the paper identifying DNA as the genetic material[1], a scientific revolution with consequences that can be viewed, in a historical perspective, as having comparable import.

At Columbia, we had heard of this research even before its publication, largely through the heralding of Alfred Mirsky from the Rockefeller Institute for Medical Research. There, Mirsky was a colleague of Oswald Avery, and embroiled in some sibling rivalry that sparked ongoing skepticism

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as to the finality of the proof that DNA, and DNA alone, was the operative molecule. Mirsky collaborated with Arthur Pollister at Columbia on studies of chromatin, a 'nucleoprotein' complex. Throughout 1944, there was some buzz about these findings, tempered by the ongoing skepticism. After all, in 1935, Wendell Stanley had proclaimed the isolation of the tobacco mosaic virus as a pure crystalline protein, an announcement that was soon to be complicated by further analyses demonstrating the presence of an RNA moiety. Not until January 20, 1945 did I actually read the text of Avery's paper[1], having borrowed a copy from Harriett Taylor – a graduate student who was about to join Avery's lab, and who was also later to meet and wed Boris Ephrussi. My reaction can only be described as a deflagration.

From my diary, Saturday January 20, 1945, 21.00h:

'... I had the evening all to myself, and particularly the excruciating pleasure of reading Avery '43 (sic) on the deoxyribose nucleic acid responsible for type transformation in *Pneumococcus*. Terrific and unlimited in its implications. Viruses are gene-type compounds, but they cannot grow on synthetic or even dead media, and their capacity for production is limited to reproduction. The TF of *Pneumococcus* has every characteristic of a mutation (should read gene)... I can see real cause for excitement in this stuff though.'

Noted in the margin:

'Direct demonstration of the multiplication of TF as well as its polysaccharide products! or the synthetic enzyme for it which may be TF itself. Dual function – reproduction – production.'

This has some garbled thinking, but there is no doubting the enthusiasm generated by Avery's publication. As recounted elsewhere[2], it set me on the path of looking for DNA transformation in *Neurospora*, and eventually to my studies of genetic recombination in *Escherichia coli*. What was important for me, and how the article changed my life, was the demonstration that genetic information could be reduced to chemical analysis. That is to say, that we were seeing the dawn of molecular genetics. Whether the agent responsible was pure DNA would be resolvable in due course; the important iconoclasm was that it could be. Once that was settled, the power of physical and chemical analysis would be brought to bear, and such further triumphs as the double-helical structure[3] were inevitable. Meanwhile, the biological interpretation of the pneumococcal transformation was somewhat foggy. Avery himself was quite reserved[1], doubtless dominated by Dobzhansky's authority in calling it an 'induced mutation', which hardly encapsulates the spirit of having captured the genes in the test tube. He was more expansive in a letter to his brother Roy on May 26, 1943 (Ref. 4):

'... are thereafter reduplicated in the daughter cells and after innumerable transfers and without further addition of the inducing agent, the same active and specific transforming substance can be recovered far in excess of the amount originally used to induce the reaction. Sounds like a virus – may be a gene. But with mechanisms I am not now concerned – one step at a time – and the first is: what is the chemical nature of the transforming principle? Someone else can work out the rest.'

It was to be many years before this letter would come to light, and it did so in parallel with universal recognition that its underlying intuitions were correct. For my part, a critical challenge was what did the pneumococcal transformation have to do with genetics, in the absence of any concrete evidence for 'genes' in bacteria. This led me to re-examine the prospects for 'playing Mendel' to *E. coli*, and the surprising realization that this venture had scarcely been tried in the 80 years since the abbot's work on garden peas. My experiments began in Ryan's lab at Columbia, and reached consummation in June, 1946, after a few months work with Ed Tatum at Yale, and the results were presented at Cold Spring Harbor in July, 1946 (Ref. 2). These results uncovered the conjugal cell-to-cell interaction in *E. coli* strain K-12. We would have been delighted if we could have promptly matched this with a DNA transformation in the same bacterium. We did get problematic inspirations from Andre Boivin, who reported exactly that at the 1947 Cold Spring Harbor symposium[5], but alas he died soon thereafter. We had no inkling of electroporation; the floodgates to direct DNA transfer in *E. coli* were only opened in 1970 with tricks no more complicated than the use of calcium phosphate gels[6]. Today, the very terminology of 'gene' is being supplanted by 'DNA sequence', and 'genetics' by 'genomics' as we are indeed moving into an undistracted, reductionist, molecular genetics.

Further bibliographic resources, and detailed documentation including many primary sources such as letters, reviews and interviews, can be found at the archival website of the National Library of Medicine at `http://profiles.NLM.nih.gov/`

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